UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,606	05/16/2006	**Susanne Moira Brown**	MWBN.CR.04	9388

25871 7590 06/11/2008

SWANSON & BRATSCHUN, L.L.C.
8210 SOUTHPARK TERRACE
LITTLETON, CO 80120

EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
06/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,606	BROWN ET AL.	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-9,11-26,31-34,36,37,42,51 and 53-70* is/are pending in the application.

4a) Of the above claim(s) *31,51,53-56,58 and 59* is/are withdrawn from consideration.

5)☒ Claim(s) *57* is/are allowed.

6)☒ Claim(s) *1-4,7-9,11-26,32-34,36,37,42 and 60-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Oath/Declaration

The oath or declaration remains defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the declaration for Paul Dunn does not refer to the specification or prior applications to which the oath or declaration is directed. See MPEP § 602.

Applicants' Declaration pursuant to 37 C.F.R. § 1.132 is not sufficient to overcome the deficiencies of the declaration. Section 409.03 of the M.P.E.P. sets forth the criteria for determining if an inventor is unavailable and sets forth the necessary proof that must be provided to the Office (see M.P.E.P. § 409.03(d) and see also 37 C.F.R. § 1.147). Applicants have not provided the necessary documentation to establish that Paul Dunn is an unavailable inventor.

Withdrawn Rejections

The rejection of claim 57 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn in view of applicants declaration regarding the availability of the claimed construct.

The rejection of claim 4 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of applicants' amendment to the claim.

The rejection of claims 1, 2, 4, 7-16, 32-34, 60 and 61 under 35 U.S.C. 102(b) as being anticipated by Coffin et al. (WO 99/38955) as evidenced by Anlezark et al. (WO 93/08288) has been withdrawn in view of applicants amendments to the claims.

The rejection of claims 17-26 under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. (WO 99/38955) as applied to claims 1, 2, 4, 7-16, 32-34, 60 and 61, and further in view of Herlitschka et al. (U.S. Patent No. 6,114,146) has been withdrawn in view of applicants amendments to the claims.

The rejection of claims 36, 37, 42 and 62-64 under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. (WO 99/38955) as applied to claims 1, 2, 4, 7-16, 32-34, 60 and 61, and further in view of Anlezark et al. (WO 108288) has been withdrawn in view of applicants amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 4 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claim is drawn to, *inter alia*, an oncolytic herpes simplex virus comprising a nucleic acid having at least 90% sequence identity to SEQ ID NO:2 or to a nucleic acid encoding the polypeptide of SEQ ID NO:1, wherein said nucleic acid encodes a protein that has nitroreductase activity.

The written description rejection is made because the claims are interpreted as being drawn to a genus of polynucleotides recited as having at least 90% identity with SEQ ID NO:2 or to a nucleic acid encoding the polypeptide of SEQ ID NO:1. The applicable standard for the written description requirement can be found in MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609; Vas- Cath Inc. v. Mahurkar, 19 USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004). To provide adequate written description and evidence of

possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is SEQ ID NO:2 (and SEQ ID NO:1) and the function of SEQ ID NO:2 (i.e., nitroreductase activity). There is no disclosure of any particular portion of the structure that must be conserved or that can be altered in order to be at least 90% identical with SEQ ID NO:2 and retain the indicated function.

The specification discloses at pages 6 and 7 that "[a]lternatively the nucleic acid may have at least 60% sequence identity to SEQ ID No. 2. Said degree of sequence identity may alternatively be one of at least 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% provided the polypeptide or protein encoded by such nucleic acid has a nitroreductase function." However, the specification does not indicate which portions of SEQ ID NO:2 are essential to retain the nitroreductase function or which portions of SEQ ID NO:2 can be modified or altered and still retain the nitroreductase function.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. A definition by function alone does not suffice to sufficiently describe a coding sequence because it is only an indication of what the gene does, rather than what it is. EliLily, 119 F.3 at 1568, 43 USPQ2d at 1406.

The court clearly states in Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed. As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of proteins that has at least 90% identity with SEQ ID NO:2. Given that the specification has only described the structure of SEQ ID NO:2 and the function of the encoded protein, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

Response to Arguments

In the reply dated February 29, 2008, applicants argue that amending claim 4 to recite a significantly smaller genus of sequences together with a recited function should be sufficient to demonstrate applicants' possession of the claimed invention. This argument is not found persuasive. See Example 10, claim 3 analysis, of the Revised Written Description Training Materials (http://www.uspto.gov/web/menu/written.pdf).

Claim 4 is directed to the genus of variants that are at least 95% identical to SEQ ID NO: 2 or to a nucleic acid encoding the polypeptide of SEQ ID NO: 1 and the variants have nitroreductase activity.

The specification discloses the reduction to practice of one species within the claimed genus; specifically, the polynucleotide having the sequence of SEQ ID NO: 2. There are no drawings or other sequences disclosed of any other polynucleotides that have nitroreductase activity.

The recitation of a polynucleotide with at least 95% amino acid sequence identity to SEQ ID NO: 2 represents a partial structure. That is, the claimed polynucleotides share at least 95% of the structure of SEQ ID NO: 2, while 5% of the structure can vary. There is no teaching in the specification regarding which 5% of the structure can be varied while retaining the ability of the polynucleotide maintain nitroreductase activity. Further, there is no art-recognized correlation between any structure (other than SEQ ID NO: 2) and the claimed activity, based on which, those of ordinary skill in the art could predict which nucleotides can vary from SEQ ID NO: 2 without losing the nitroreductase activity. Consequently, there is no information about which nucleotides can vary from SEQ ID NO: 2 in the claimed genus of polynucleotides and still retain the nitroreductase activity.

Although the disclosure of SEQ ID NO: 2 combined with the knowledge in the art, would put one in possession of polynucleotides that are at least 95% identical to SEQ ID NO: 2, the level of skill and knowledge in the art is such that one of ordinary skill would not be able to identify without further testing which of those polynucleotides having at least 95% identity to SEQ ID NO: 2 (if any) have the claimed activity. Based on the lack of knowledge and predictability in the art, those of ordinary skill in the art

would not conclude that the applicant was in possession of the claimed genus of proteins based on disclosure of the single species of SEQ ID NO: 2.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "substantially resembles" in claims 65 and 67 is a relative phrase which renders the claim indefinite. The phrase "substantially resembles" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7-9, 12-16, 32-34, 60, 61 and 65-70 are rejected under 35 U.S.C. 102(b) as being anticipated by Coffin et al. (WO 01/53506).

The claims are drawn to, *inter alia*, an oncolytic herpes simplex virus wherein the herpes simplex virus genome comprises nucleic acid encoding an heterologous nitroreductase (NTR), wherein the genome has an inactivating mutation in the RL1 locus such that the herpes simplex virus does not produce a functional ICP34.5 gene product, and wherein the herpes simplex virus is a mutant of one of HSV-1 strains 17 or F or HSV-2 strain HG52.

Coffin et al. discloses oncolytic herpes viral genomes comprising a heterologous gene, which can be nitroreductase (see page 17, line 25 to page 18, line 4 and lines 17-29, and page 29, line 15 to page 31, line 8).

The constructs of Coffin et al. further comprise a regulatory sequence (i.e., promoter) operably linked to the nucleic acid encoding the NTR (see page 24, line 22 to page 25, line 14). The ICP34.5 gene or ICP6 gene (ribonucleotide reductase) of HSV can be rendered functionally inactive by deletions, substitutions or by inserting the heterologous gene within the ICP34.5 sequence (see page 17, line 25 to page 18, line 4). Coffin et al. teaches the use of HSV strains 17+ and F (see page 29, line 15 to page 31, line 8). One or more copies of ICP34.5 can be rendered dysfunctional or deleted (see page 17, lines 25 to page 18, line 16). Further, the HSV can be non-neurovirulent after inactivation of ICP34.5 (see page 29, lines 17-21). Furthermore, the constructs of Coffin et al. can be formulated as a pharmaceutical composition (see page 28, lines 10-13).

Therefore, Coffin et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. (WO 01/53506) as applied to claim 1 above, and further in view of Anlezark et al. (WO 93/08288) or Perna et al. (Nature, 2001, 409:529-533).

Coffin et al. teaches that further enhanced activity may also be anticipated if these viruses are then used to deliver heterologous genes with anti-tumor activity. Such genes include those encoding pro-drug activators, such as nitroreductase. Coffin et al. does not specifically teach a nitroreductase from *E. coli* or a nucleic acid encoding the polypeptide of SEQ ID NO:1.

However, Anlezark et al. discloses *E. coli* nitroreductase polypeptides that are capable of converting a precursor pro-drug into a cytotoxic compound. The nitroreductase of Anlezark et al. is 97% identical to instant SEQ ID NO:2.

Perna et al. teaches the amino acid sequence of an *E. coli* nitroreductase (instant SEQ ID NO:1) (see attached alignment).

It would have been obvious to one of ordinary skill in the art to modify construct of Coffin et al. and substitute any known nitroreductase including the nitroreductase taught by Anlezark et al. and the results would have been predictable. Further, one of ordinary skill in the art can deduce the nucleotide sequence for the nitroreductase amino acid sequence taught by Perna et al. (instant SEQ ID NO:1). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. (WO 01/53506) as applied to claim 1 above, and further in view of Coukos et al. (Clinical Cancer Research, 1999, 5:1523-1537).

Coffin et al. does not specifically teach the use of HSV-1 strain mutant 1716 in the design of its oncolytic HSV constructs. However, Coukos et al. discloses that HSV-1716, a replication-competent attenuated strain lacking ICP34.5, caused a direct dose-dependent oncolytic effect on epithelial ovarian cancer cells (see, for example, the abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to modify construct of Coffin et al. and substitute HSV mutant 1716 in the construct of Coffin et al. and the results would have been predictable, as 1716, with IPC34.5 deleted, has been shown to be effective against cancer cells.

Claims 17-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. (WO 01/53506) as applied to claim 1 above, and further in view of Herlitschka et al. (U.S. Patent No. 6,114,146).

The claims are drawn to an oncolytic herpes simplex virus comprising a nucleic acid cassette integrated in the genome of said herpes simplex virus, said cassette encoding:

(a) said nucleic acid encoding NTR;

(b) nucleic acid encoding a ribosome binding site; and

(c) a marker,

wherein the nucleic acid encoding NTR is arranged upstream (5') of the ribosome binding site and the ribosome binding site is arranged upstream (5') of the marker.

In addition to the teachings of Coffin et al. outlined above, Coffin et al. also teaches an expression cassette comprising one or more heterologous genes, where one gene can be NTR and the other gene can be a marker such as GFP and each gene can have its own promoter (see page 25, lines 15-18 and page 26, lines 7-11). The constructs of Coffin et al. can optionally include the associated transcriptional control sequences normally associated with the transcribed sequences, for example

transcriptional stop signals, polyadenylation sites and downstream enhancer elements (see page 24, lines 7-12).

Coffin et al. does not teach use of a ribosome binding site, the arrangement of the cassette and use of the SV40 polyadenylation signal. However, Herlitschka et al. discloses a dicistronic expression cassette comprising a foreign gene, a fusion gene comprising a marker and a ribosome binding site located between the foreign gene and the marker gene. According to a preferred embodiment, the encoding sequence for the foreign protein lies 5' and the encoding sequence for the fusion protein lies 3' from the internal ribosome binding site. This arrangement enables a maximum yield of foreign protein, since the gene for the foreign protein is located immediately downstream of the promoter and thus is optimally transcribed (see col. 5, lines 48-65). Further, Herlitschka et al. states that "[t]o keep the coupling of the marker gene with the foreign protein while reducing rearrangements and deletions, attempts have been made to introduce sequence elements between the dicistronic reading frames, to which sequence elements ribosomes can bind internally." (see col. 3, lines 35-42). Herlitschka et al. also teaches the use of the SV40 polyadenylation signal in its constructs (see the Examples).

It would have been obvious to one of ordinary skill in the art to modify the construct of Coffin et al. to include a ribosome binding site between the NTR and marker genes. One would have been motivated to do so given the suggestion by Herlitschka et al. that this type of arrangement enables maximum yield of foreign protein, since the gene for the foreign protein is located immediately downstream of the

promoter and thus is optimally transcribed. There would have been a reasonable expectation of success given the fact that Herlitschka et al. successfully produced expression cassettes with a ribosome binding site between the foreign gene and the marker gene. It also would have been obvious to include the SV40 polyadenylation signal because it is well known and routine to do so (see Herlitschka et al. Examples). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 36, 37, 42 and 62-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coffin et al. (WO 01/53506) as applied to claims 1 and 34 above, and further in view of Anlezark et al. (WO 93/08288).

The claims are drawn to a composition or kit comprising the herpes simplex virus and an NTR prodrug such as CB1954.

Coffin et al. teaches that further enhanced activity may also be anticipated if these viruses are then used to deliver heterologous genes with anti-tumor activity (see page 4, lines 6-9). Such genes include those encoding pro-drug activators, such as nitroreductase. Polypeptides that are capable of converting a precursor prodrug into a cytotoxic compound include bacterial nitroreductase such as *E. coli* nitroreductase as disclosed in WO 93/108288. WO 93/108288 (Anlezark et al.) teaches compositions comprising nitroreductase and the prodrug CB1954 (see, for example, page 11, lines 10-21 and page 12, lines 30-35 of Anlezark et al.) for treating cancer.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the constructs of Coffin et al., which encode NTR, with a prodrug such as CB1954 as taught by Anlezark et al. One would have been motivated to do so and there would have been a reasonable expectation of success given the teachings of Anlezark et al. (At page 11, lines 10-13: One of the most important practical applications of the new enzymes (nitroreductase) of the present invention is that they can be used in association with nitro compounds (CB1954) that are prodrugs for anti-tumor agents and so provide a system of cancer chemotherapy).

As for the kit claims, it would have been obvious to one of ordinary skill in the art at the time the invention was made to package components into a kit. One would be motivated to do this for commercial exploitation of the invention by providing convenience for the end user.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claim 57 is allowable.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White, PhD/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648